REMARKS

In view of the foregoing amendments, reconsideration and re-examination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §112 are respectfully requested. By the present amendments, the claims have been amended to expedite prosecution of the subject application. Entry of the amendments is respectfully requested.

Turning now to the Official Action the objection to the Declaration is noted. Applicants will submit a new Declaration forthwith.

Indication in the Official Action that certain previous grounds of rejection have been withdrawn is noted with appreciation. It is respectfully submitted that in light of the above amendments, all rejections and objections should be withdrawn and such favorable action is respectfully requested.

Claims 1, 2, 4-9, 24-29, 34, 36 and 37 stand rejected under 35 U.S.C. §112, second paragraph for alleged indefiniteness. This rejection is respectfully traversed for at least the following reasons.

In the Official Action it is objected to the recitation "desired binding specificity" and "desired specificity," for alleged lack of clarity. This objection is believed to be rendered moot by the above amendments whereby the allegedly objectionable language has been removed to expedite the prosecution of the application.

The Official Action objects to the recitation "C2B8 p5E8." This rejection is respectfully traversed for at least the following reasons. It is respectfully submitted that the specification in light of the record in the subject application provide ample guidance to those of skill in the art to recognize the heterodimer C2B8 p5E8 as claimed in the present application. In particular, it [illegible] the subject specification and the C2B8 and the p5E8 antibody molecules [illegible] discussion thereof in the specification provide an illustration of how the C2B8

and p5E8 molecules are combined to provide antibody heterodimers in accordance with the subject invention. Thus, withdrawal of the objection is respectfully requested.

Claims 1, 2, 4-9, 24-29, 34, 36, 37, 45 and 46 stand rejected under 35 U.S.C. §112 first paragraph for alleged non-enabling specification. This rejection is respectfully traversed for at least the following reasons.

At the outset, Applicants note the acknowledgement in the Official Action that the subject specification is enabling for a method for producing a IgG antibody heterodimer with antibodies which specifically bind CD20 and CD23. However, Applicants strenuously traverse the conclusion reached in the Official Action that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims. In this regard, it is respectfully submitted that those of skill in the art will recognize that the subject invention relates to antibody dimers that are formed by connecting two (2) antibody molecules, each molecule having binding affinity to an antigen. The binding affinity of the two molecules forming the dimer may be to the same antigen (homodimer) or two different antigens (heterodimer) as is claimed in the subject application. The specification in its entirety, and particularly the examples provide ample guidance on how to prepare dimers according to the invention such that the resulting heterodimer is prepared at a high purity and with relatively high yields.

Moreover, by the above amendments, the claims have now been revised to recite an antibody heterodimer composed of two **different antibody molecules** having binding specificity to **two distinct antigens** by a method comprising obtaining or constructing a DNA molecule that encodes an

[illegible] wherein the

location of the cysteine does not interfere with the antigen binding

properties of the heterodimer; expressing said DNA molecule in a suitable host cell, or expression system, together with a DNA molecule that encodes an **antibody molecule light chain of the same specificity** as the heavy chain, to produce an antibody molecule containing said introduced cysteine residue; contacting said purified antibody molecule with an amount of a suitable reducing agent sufficient to partially reduce the intra or inter molecular disulfide bonds of said antibody molecule and thereby enhance the formation of antibody dimers; and contacting the purified antibody molecule with **another antibody molecule having antigen specificity other than the antigen specificity of the first antibody molecule** and which does not have a cysteine group introduced therein; and allowing sufficient time for the dimerization reaction to proceed; thereby producing said antibody heterodimer.

It is respectfully submitted that the claims as now presented clearly exclude embodiments wherein the cysteine residue would be located in a position detrimental to the formation of antigen binding heterodimers according to the invention.

In addition, Applicants reiterate that the Examiner's position that "undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone" is improper in view of the standards for enablement, as addressed by the CAFC in the case of *in re Brana*, 551 F.3d 1560; 34 U.S.P.Q.2d 1437 (CFC, decided March 30, 1995). In *in re Brana*, the CAFC held that:

> A specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken [illegible] with the enabling requirement of [illegible] therein which must be relied on for enabling support. *In re Marzocchi*, 58 C.C.P.A. 1069, 439

F.2d 220, 223, 169 U.S.P.Q. 367, 369 (CCPA 1971). From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure.

In summary, the essence of the court's decision was that if the patent disclosure contains a teaching of how to make and use an invention which is commensurate with the scope of the claims and further provides a specific working example in support of the stated utility, then further evidence should not be required to satisfy the enablement requirement of §112, first paragraph, unless there is reason to doubt the objective truth of the statements contained in the disclosure which are relied on for enabling support. Applicants submit that the present disclosure fully satisfies the enablement standard set forth in *in re Brana* in that it provides sufficient teaching of how to make the antibody heterodimers of the invention.

Claims 1, 2, 4-9, 24-29, 34-37, 41, and 45-49 were newly rejected under 35 U.S.C. §112 second paragraph for allegedly failing to set forth the subject matter which applicants regard as their invention. This rejection is respectfully, but strenuously, traversed for at least the following reasons.

The Official Action improperly relies on the statement by Applicants' representative in the previous Reply indicating that "by using special conditions (i.e., purifying the selectively reduced monoclonal antibody by applying it to PD-10; and equilibrating with the oxygenated normal saline containing sodium citrate, which discourages the formation of homodimer via disulfide bond) one can be assured that only dimers formed by thioether linkage are produced" to infer that these conditions are required to practice the subject invention, and must therefore be recited in the claims. However, it is [illegible] from the specification that the cited

[illegible] specification. The statement relied upon in the Official Action is taken from a

larger context set forth in a section of the specification on pages 11-17 where the method of the invention is distinguished from the Ghetie method based on illustrative embodiments of the invention which cannot properly be used to limit the scope of the claims in the subject application. Withdrawal of the requirement to include the illustrative conditions in the claims is in order and is respectfully requested.

In light of the foregoing, it is respectfully submitted that the specification and claims are free of the rejections under 35 U.S.C. §112 first and second paragraphs. Thus, withdrawal of the rejections is in order and respectfully requested.

Prior to addressing the art rejections set forth in the Official Action, Applicants submit the following summary of the invention and the advantages thereof. As extensively discussed in the specification, the present invention generally relates to a process for the preparation of biologically active antibody dimers and pharmaceutical compositions containing such antibody dimers. The process of the invention provides numerous advantages. For example, the process of the invention provides for antibody dimers with an increased yield and much higher purity compared to conventional methods of producing antibody dimers. In part, the advantages of the invention are obtained by using monoclonal antibodies which had had a cysteine residue genetically engineered at a specific site on the F_c arm of the antibody, thereby eliminating the need to chemically introduce the reactive group. As indicated in the specification, yields of homodimer formation of between 40 to 50% of the starting material are obtained with the method of the invention. Also, surprisingly and unexpectedly, when compared to antibody dimers made by conventional methods, dimers produced by the claimed process were capable of initiating

culture, showing a two hundred fold increase in potency compared to that of a dimer prepared according to conventional methods.

In an effort to expedite prosecution of the subject application, the claims have been revised to recite a method for producing an antibody heterodimer composed of **two different antibody molecules** having binding specificity to **two distinct antigens** by a method comprising obtaining or constructing a DNA molecule that encodes an antibody molecule heavy chain that has binding specificity and introducing at least one cysteine codon via recombinant DNA mutagenesis, **wherein the location of the cysteine does not interfere with the antigen binding properties of the heterodimer;** expressing said DNA molecule in a suitable host cell, or expression system, together with a DNA molecule that encodes an **antibody molecule light chain of the same specificity as the heavy chain**, to produce an antibody molecule containing said introduced cysteine residue; contacting said purified antibody molecule with an amount of a suitable reducing agent sufficient to partially reduce the intra or inter molecular disulfide bonds of said antibody molecule and thereby enhance the formation of antibody dimers; and contacting the purified antibody molecule with **another antibody molecule having antigen specificity other than the antigen specificity of the first antibody molecule** and which does not have a cysteine group introduced therein; and allowing sufficient time for the dimerization reaction to proceed; thereby producing said antibody heterodimer. Applicants urge that the references of record, neither alone nor in combination, do not disclose or suggest the invention as presently claimed.

Claims 2, 4, 28, 41, and 46 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Brennan et al (Science 229: 81-83, 1985). This rejection is respectfully traversed for at least the following reasons.

antibody heterodimer composed of **two different antibody molecules** having

binding specificity to two distinct antigens. Brennan appears to be directed to one antibody molecule having bispecificity. Thus, Brennan et al cannot and does not anticipate the invention as presently claimed. Thus, the 102 rejection is improper and should be withdrawn. Such favorable action is respectfully requested.

Claims 1, 2, 4-9, 14, 24-29, 34-37, 41 and 45-49 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Caron et al. (*J. Exp. Med.* 176: 1191-1195 (1992)) and further in view of Fanger et al. (*Critical Review in Immunology* 12: 101-124 (1992)) and Cumber et al. (*J. of Immunol.* 149: 120-126 (1992) and Reff et al. [a] (US Patent No. 6,011,138) and Reff et al. [b] (Blood 83: 435-445 (1994)). This rejection is respectfully traversed for at least the following reasons.

Even combined as suggested in the Official Action, the references fail to suggest a method for producing an antibody heterodimer composed of two **different antibody molecules** having binding specificity to **two distinct antigens** by obtaining or constructing a DNA molecule that encodes an antibody molecule heavy chain that has binding specificity and introducing at least one cysteine codon via recombinant DNA mutagenesis, **wherein the location of the cysteine does not interfere with the antigen binding properties of the heterodimer;** expressing said DNA molecule in a suitable host cell, or expression system, together with a DNA molecule that encodes an **antibody molecule light chain of the same specificity** as the heavy chain, to produce an antibody molecule containing said introduced cysteine residue; contacting said purified antibody molecule with an amount of a suitable reducing agent sufficient to partially reduce the intra or inter molecular disulfide bonds of said antibody molecule and thereby enhance the formation

another antibody molecule having antigen specificity other than the **antigen specificity of the first antibody molecule** and which does not have a

cysteine group introduced therein; and allowing sufficient time for the dimerization reaction to proceed; thereby producing said antibody heterodimer. Therefore, the combined references fail to appreciate the advantages of the invention as discussed above.

Thus, there is no *prima fascia* case of obviousness against the present claims based on Caron et al. alone or in combination with Fanger et al., Cumber et al., Reff et al. [a] and Reff et al. [b]. Accordingly, the rejection under 35 U.S.C. §103(a) based on those documents should be withdrawn and such favorable action is respectfully requested.

From the foregoing, it is anticipated that this response should place this case in condition for allowance. A notice to that effect is respectfully solicited. However, if any issues remain outstanding, the Examiner is respectfully requested to contact the undersigned so that prosecution may be expedited.

Respectfully submitted,

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APPENDIX

In the Claims:

Please enter the following amended Claims:

1. A method for producing an antibody heterodimer composed of two different antibody molecules having binding specificity to two distinct antigens, [comprising] wherein the method comprises:

(vi) obtaining or constructing a DNA molecule that encodes an antibody molecule heavy chain that has [desired] binding specificity and introducing at least one cysteine codon via recombinant DNA mutagenesis, wherein the location of the cysteine does not interfere with the antigen binding properties of the heterodimer;

(vii) expressing said DNA molecule in a suitable host cell, or expression system, together with a DNA molecule that encodes an antibody molecule light chain of [desired] the same specificity as the heavy chain, to produce an antibody molecule containing said introduced cysteine residue;

(viii) purifying said antibody molecule from said host cell or expression system;

(ix) contacting said purified antibody molecule with an amount of a suitable reducing agent sufficient to partially reduce the intra or inter molecular disulfide bonds of said antibody molecule and thereby enhance the formation of antibody dimers; and

(x) contacting the purified antibody molecule with another antibody

[illegible] specificity to the antibody molecule of [illegible] specificity

which does not have a cysteine group introduced therein; and

allowing sufficient time for the dimerization reaction to proceed: thereby producing said antibody heterodimer.

24. A method for producing an antibody heterodimer composed of two different antibody molecules having binding specificity to two distinct antigens, [comprising] wherein the method comprises:

(vi) obtaining or constructing a DNA molecule that encodes an antibody molecule heavy chain that has [desired] binding specificity and introducing at least one cysteine codon therein via recombinant DNA mutagenesis, wherein the location of the cysteine does not interfere with the antigen binding properties of the heterodimer;

(vii) expressing said DNA molecule in a suitable host cell, or expression system, together with a DNA molecule that encodes an antibody molecule light chain of [desired] the same specificity as the heavy chain, to produce an antibody molecule containing said introduced cysteine residue;

(viii) purifying said antibody molecule from said host cell or expression system;

(ix) contacting said purified antibody molecule with an amount of a suitable reducing agent sufficient to partially reduce the intra or inter molecular disulfide bonds of said antibody molecule and thereby enhance the formation of antibody dimers; and

(x) adding a thiol reactive group introduced on another antibody molecule having antigen specificity other than the antigen specificity of the antibody molecule purified in step (iii) and

thereby producing said antibody heterodimer.

37. A method for producing an antibody heterodimer composed of two different antibody molecules having binding specificity to two distinct antigens, [comprising] wherein the method comprises [comprising]:

(i) obtaining a DNA molecule that encodes an antibody molecule heavy chain that has [desired] binding specificity and introducing at least one cysteine codon via recombinant DNA mutagenesis, wherein the location of the cystein does not interfere with the antigen binding properties of the heterodimer;

(v) expressing said DNA molecule in a suitable host cell, or expression system, together with a DNA molecule that encodes an antibody molecule light chain of [desired] the same specificity as the heavy chain, to produce an antibody molecule containing said introduced cysteine residue;

(vi) purifying said antibody molecule from said host cell or expression system;

(vii) contacting said purified antibody molecule with an amount of a suitable reducing agent sufficient to partially reduce the intra or inter molecular disulfide bonds of said antibody molecule and thereby enhance the formation of antibody dimers; and

cross-linking the reduced antibody molecules using a BIS-maleimido crosslinker thereby producing said antibody heterodimer.